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Comparative effect of Initiating Metformin versus Sulfonylureas on Breast Cancer Risk in Older Women

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Abstract

Background—Several observational studies have reported that metformin may be associated with reduced risk of breast cancer; however, many of these studies were affected by time-related biases such as immortal time bias and time-window bias. This study aimed to examine the relative

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The code is provided on request. Our Medicare data are not available for replication because of the data use agreement, but can be obtained from the Centers for Medicare & Medicaid Service.

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risk of breast cancer for older women initiating metformin versus sulfonylureas while avoiding such biases.

Methods—The study cohort consisted of women aged 65+ who initiated monotherapy with metformin (n=45,900) or sulfonylureas (n=13,904) and were free of cancer and renal disease within 6 months before treatment initiation using 2007–2012 US Medicare claims data. We followed treatment initiators for incident breast cancer, and estimated hazard ratios using weighted Cox models. Unmeasured confounding by body mass index and smoking was further adjusted by propensity score calibration using external information from Medicare Current Beneficiary Survey 2006–2009 panels.

Results—During 58,835 and 16,366 person-years of follow-up, 385 initiators of metformin treatment and 95 of sulfonylurea were diagnosed with breast cancer. Metformin initiators did not have a reduced risk of breast cancer compared with sulfonylurea initiators (hazard ratio: 1.2; 95% confidence interval: 0.94, 1.6). Externally controlling for body mass index and smoking did not affect the estimates.

Conclusion—The findings of this study provide no support for a reduced risk of breast cancer after initiation of metformin compared with a clinical alternative in older women. This study is limited by the relatively short follow-up time and we cannot exclude the possible benefits of long-time metformin use on breast cancer risk.

Keywords

Metformin; Diabetes; Breast Cancer

Breast cancer is the most common cancer and is the second leading cause of cancer death for women in the United States. The cost of breast cancer care in 2010 was estimated at 16.5 billion dollars in US, the highest among all cancer sites.[2] Diabetes is associated with a 20%-40% increased risk of breast cancer in women.[3] As the first-line treatment for type 2 diabetes [4], metformin has received much attention due to its potential to reduce cancer incidence and improve outcomes, in particular, for breast cancer.[5–7]

Evidence from preclinical and clinical studies suggests that metformin has anti-tumor properties and may reduce incidence and mortality of breast cancer.[9,10] A meta-analysis of seven observational studies found a 17% decreased risk of breast cancer associated with metformin, and reported that metformin use for 3 years or longer was associated with 25% reduced risk of breast cancer.[11] Despite several observational studies suggesting chemopreventive effects of metformin on breast cancer, concerns have been raised that many of these studies were subject to time-related biases (e.g., immortal time bias and time-window bias) which would lead to an apparent protective effect in the absence of a real effect or magnify any potential beneficial effect of metformin on cancer incidence.[12]

Apart from time-related bias, unmeasured confounding is another major potential source of bias in observational studies, especially those based on claims data. Claims data are not collected for research purposes and usually lack information on some risk factors for breast cancer in postmenopausal women, such as body mass index (BMI) and smoking.[13–15] Unmeasured confounding by BMI and smoking is a major concern in studies comparing

metformin users with non-users. In studies comparing metformin initiators with initiators of a clinical alternative for patients with type 2 diabetes, the potential for unmeasured confounding by BMI and smoking is largely reduced.

Observational studies are useful to evaluate drug safety and effectiveness in real world settings.[16,17] If incorrectly designed, however, they can suffer from various types of biases leading to spurious results. For example, observational findings on benefits of statins in patients with chronic obstructive pulmonary disease were recently disproved by a randomized trial.[18] The discordance between observational studies and randomized trials is often portrayed as being the results of a fatal flaw inherent to observational studies, but such a view ignores the fact that not all observational studies are created equal. Observational studies need to be designed using rigorous methods to reduce the potential for bias.[12,19,20] Our objective was to investigate whether metformin reduces the risk of breast cancer in a large, nationally representative older population in the US, by conducting a state-of-the-art new user cohort study with a clinical alternative.[20]

METHODS

Study population

Our study cohort was selected from women aged 65 years or older enrolled in Medicare between 2007 and 2012. Medicare is the United States federal health insurance plan, administered by the Centers for Medicare and Medicaid Services. Medicare provides medical coverage for citizens aged 65 years or older, with certain disabilities, or with End-Stage Renal Disease (ESRD). The Medicare database is composed of Part A (inpatient), Part B (outpatient physician services), and Part D (dispensed prescription drugs) claims and also contains patients' demographics. Our study cohort included only new users of metformin and sulfonylureas. To be eligible as a new user, women were required to be aged 65 years or older, to have had at least 6-month continuous enrollment in Medicare Parts A, B, and D before initiation, and to have initiated monotherapy with metformin or sulfonylureas after at least 6 months without a prescription for any anti-hyperglycemic drugs. Given that metformin and sulfonylureas were primarily indicated for diabetes in the elderly, we assumed that patients receiving metformin or sulfonylureas were diagnosed with diabetes, thus not restricting the study cohort to those with a prior diagnosis code for diabetes. Initiation was defined as not having received any anti-diabetic treatment within 6 months prior to the first prescription of metformin or sulfonylureas and having had at least 1 refill within 90 days after the end of days-supply of the first prescription. The date of the first refill was defined as the index date. Patients were excluded if they had a prior diagnosis of renal disease or cancer during the 6 months before the index date. Patients with renal disease were excluded because metformin is contraindicated in these patients.[4] The flowchart of study population is shown in eFigure 1.

Follow-up for breast cancer

The outcome of interest was a diagnosis of incident breast cancer during follow-up, including both *in situ* and invasive breast cancer, identified by having at least two ICD-9 diagnosis codes for breast cancer on different dates within 60 days. The date of the first

diagnosis was used to define the outcome date. This algorithm has been previously validated in a Medicare population.[21]

We used both as-treated (primary) and intention-to-treat (secondary) analyses. Because breast cancer has a long preclinical phase, we assumed a 180-day induction period for cancer pathogenesis and a 180-day carry-over effect or latency period for cancer detection in the analysis. The as-treated approach defined follow-up based on actual exposure to the initial treatment. Patients were considered to be exposed to the initial treatment (i.e., metformin or sulfonylureas) until treatment changes. Treatment changes included drug discontinuation, switch to or a subsequent addition of other anti-diabetic drug classes to the index prescription. Treatment discontinuation was defined as no further refill within the days supply plus a 90-day grace period. To account for induction and latency periods, follow-up started on 180 days after the index date, and ended with the earliest of the following events: 180 days after treatment changes, any cancer diagnosis except for non-melanoma skin cancer, death, enrollment gap in Medicare Part A, B, and D enrollment greater than 1 month, or end of study (31 December 2012). In the intention-to-treat analysis (first treatment carried forward), patients were considered to be exposed to the initial treatment until administrative censoring, ignoring any subsequent treatment changes. It followed patients from 180 days after the index date and until the date of any cancer diagnosis except for non-melanoma skin cancer, death, enrollment gap in Medicare Part A and B enrollment greater than 1 month, or end of study, irrespective of any treatment change or discontinuation.

Confounding control

We used propensity scores to control for measured confounding.[22] For each patient, the probability of receiving metformin vs sulfonylureas was estimated using a logistic regression model (i.e., the propensity score model). The propensity score model included demographic and clinical variables that we identified as potential confounders or risk factors for breast cancer, as well as frequencies of healthcare utilization. All covariates were defined based on available information during the 6-month period prior to initiation. We standardized the distribution of these covariates to that of the metformin initiators using weights of 1 for metformin initiators and the odds of propensity score for sulfonylurea initiators.[23]

Statistical analysis

We summarized baseline characteristics by study cohort and further adjusted them by propensity score weighting. For each treatment group, we estimated the crude and weighted incidence rates for breast cancer using a Poisson regression model. We then used a Cox proportional regression model to estimate the crude and weighted hazard ratios (HRs) of breast cancer with 95% confidence intervals (CIs) using a robust variance estimation for the weighted model. To explore potential trends of the HRs over time, we estimated the HRs in sequential 6-month intervals following the index date. We also performed subgroup analyses, stratified by age group, race, and baseline use of statins.

Several sensitivity analyses were pre-planned. First, given the unresolved concerns as to whether sulfonylureas have an effect on breast cancer risk, we compared the risk of breast cancer in new users of metformin vs two alternative active comparator groups: (1) new users

of thiazolidinediones or dipeptidyl peptidase-4 inhibitors, both of which are also oral hypoglycemic agents; (2) diabetic patients who initiated angiotensin-converting-enzyme inhibitors without prior use of any anti-diabetic drugs. Second, to minimize the potential misclassification in defining treatment use during follow-up and diabetic patients, we repeated the primary analyses with a longer grace period of 180 or 365 days and restricting to new users who had a diagnosis code for diabetes within 6 months before initiation, respectively. Because detection of early renal disease might be differential between treatment cohorts, we conducted an analysis including prior renal disease and an analysis excluding those patients with severe renal disease (i.e., chronic kidney disease stage 4 and 5). Additionally, we restricted the outcome of interest to invasive breast cancer only. Finally, to evaluate the robustness of the assumptions of induction and latency periods, we repeated the main analysis while varying the induction period from 0 to 365 days (for both the as-treated and intention-to-treat analysis) and the latency period from 0 to 730 days (for the as-treated analysis).

External Validation Study

To quantify the extent of residual confounding by BMI and smoking that are unavailable in Medicare claims, we conducted a cross-sectional study using external data from the Medicare Current Beneficiary Survey (MCBS) 2006–2009 panels to identify women initiating metformin or sulfonylureas. The MCBS is a survey conducted within a sample of the Medicare population. The MCBS participants were sampled to be generally representative of the Medicare population but with an oversampling of the disabled and the oldest-old (85 years of age or over). New use was defined as initiation of monotherapy with metformin or sulfonylureas after at least 6 months without a prescription for metformin or sulfonylureas. Given the sample size of the MCBS is relatively modest and therefore that the absolute number of women initiating these drugs is small in the MCBS, initiation was defined by requiring only one prescription. We extracted data on height, weight, and self-reported smoking status from the MCBS Cost & Use module in the same year of initiation. BMI was calculated by weight (kilogram) divided by height (meter) squared, and was treated as a continuous variable as well as a categorical variable (<25 as normal; ≥25 and <30 as overweight; and ≥30 as obese). Individual smoking status was grouped into never and ever smoker. History of comorbidity and co-medication at baseline were retrieved from the linked Medicare claims data. We quantified the association of BMI and smoking with the initiation of metformin vs sulfonylureas independent of other covariates, fitting a propensity score model equivalent to the one in the Medicare study as far as possible, because the small number of initiators in the MCBS limited the number of covariates that could be included in logistic regression models.

We implemented propensity score calibration to correct the effect estimates in the Medicare study for confounding by BMI and smoking.[25,26] Briefly, two propensity scores were estimated within the MCBS data: the error-prone propensity score based on covariates available in claims, and the gold-standard propensity score based on BMI and smoking status in addition to the variables available in claims. Based on these two propensity scores in the MCBS study and the estimates from the Cox model in the Medicare study, we applied

regression calibration to correct regression coefficients in the Medicare cohort using the SAS macro "%blinplus."[27]

All statistical analyses were performed with the SAS 9.3 (SAS Institute, Cary NC). This study was approved from the Institutional Review Board (IRB) expedited review at the University of North Carolina at Chapel Hill.

RESULTS

We identified 45,900 and 13,904 women who initiated metformin or sulfonylureas who met our inclusion criteria, respectively. Compared with metformin initiators, sulfonylurea initiators were older, had more cardiovascular disease (i.e., congestive heart failure and ischemic heart disease), and were more likely to have been admitted to a hospital and visited an emergency room in the 6 months prior to the index date (Table 1). Metformin initiators were more likely to have received a prescription for statins, a mammogram, or a lipid test compared with sulfonylurea initiators. After propensity score weighting, the marginal distributions of measured characteristics were comparable between women initiating metformin and sulfonylureas.

In our primary, as-treated analysis, 385 metformin initiators and 95 sulfonylurea initiators were diagnosed with breast cancer over 58,835 and 16,366 person-years of follow-up, respectively (Table 2). The crude incidence rates of breast cancer per 1,000person-years were 6.5 (95% CI: 5.9, 7.2) and 5.8 (95% CI: 4.7, 7.1) in metformin and sulfonylureas initiators, respectively. After propensity score weighting the sulfonylurea initiators to minimize any measured baseline differences between the treatment groups, the incidence rate was 5.5 (95% CI: 4.9, 6.2) in sulfonylureas initiators. The weighted HR comparing metformin with sulfonylureas initiators was 1.2 (95% CI: 0.94, 1.6) (Table 2). The effect estimate from the intention-to-treat analysis was unchanged (adjusted HR: 1.2; 95% CI: 0.96, 1.4).

In Figure 1A, we examined the risk of breast cancer associated with metformin stratified by duration of treatment after initiation. No decreasing trend was observed after initiation and HR estimates were all close to the null. Figure 1B shows the breast cancer risk for metformin *vs* sulfonylureas initiators across several subgroups. There was no indication of a protective association across the age groups and in either subgroup defined by prior statin use. However, we observed a possibly reduced risk for breast cancer associated with metformin in black women (HR: 0.79; 95% CI: 0.39, 1.6, for the as-treated analysis) but the confidence interval was wide due to the small number of events (n=36 for the as-treated analysis). The results were similar in the as-treated and intention-to-treat analyses (eFigure 4). We also conducted several sensitivity analyses. No association with breast cancer was observed when comparing metformin initiators to initiators of thiazolidinediones or dipeptidyl peptidase-4 inhibitors or to diabetic initiators of angiotensin-converting-enzyme inhibitors (eTable 1). Similarly, metformin was not associated with a lower risk of breast cancer while varying the length of the induction period, the latency period, or the grace period (eTable 2–4).

We further controlled for unmeasured confounding by BMI and smoking with propensity score calibration. A total of 118 and 79 female initiators of metformin and sulfonylureas were identified from the MCBS. Being obese (BMI: ≥30) and ever smoking were associated with metformin initiation (Table 3). These associations were diminished after multivariable adjustment (mainly driven by age effects), indicating little difference in associations with BMI and smoking status conditional on controlling for other differences. Thus, the hazard ratio for breast cancer comparing metformin *vs* sulfonylureas remained unchanged after the propensity score calibration correction (eTable 5).

DISCUSSION

In this large, population-based study using an active comparator, new-user cohort design we found that older women initiating metformin did not have a lower risk for breast cancer than women initiating a therapeutic alternative. The findings were consistent across all sensitivity analyses. Despite our observation of a possible tendency towards a lower risk of breast cancer associated with metformin in African American women, our result showing no beneficial association was consistent across several subgroup and sensitivity analyses.

Several studies have reported a lower risk of breast cancer associated with metformin, but may have suffered from time-related biases.[28–30] The greatest benefits of metformin on reducing breast cancer risk were observed in a case-control study conducted within the Clinical Practice Research Datalink (CPRD).[28] Long-term use of metformin (≥ 40 prescriptions) was associated with a marked reduction in breast cancer risk compared with no use of metformin (Odds Ratio (OR): 0.44; 95% CI: 0.24, 0.82). A case-control study from Denmark reported a reduced risk of breast cancer comparing ≥ 1-year use of metformin to both no use of metformin (OR: 0.81; 95% CI: 0.63, 0.96) and use of other anti-diabetic drugs (OR: 0.78; 95% CI: 0.59, 1.0).[29] A beneficial association with metformin was also observed in women with 5 years of metformin use (OR: 0.83; 95% CI: 0.56, 1.2) and among women with diabetes complications (OR: 0.67; 95% CI: 0.45, 1.0).[29] Metformin may have benefits on breast cancer risk after long-term use, but at least part of these inverse associations may also be due to time-window bias.[12] This type of bias arises from unequal time windows of exposure opportunity between cases and controls because cases and controls were not matched on time since onset of diabetes or since the first antidiabetic prescription in this study.

Our null results are consistent with most of prior studies not affected by time-related biases. Three cohort studies, all using the UK Clinical Practice Research Datalink (CPRD), found no association of metformin versus sulfonylureas with the risk of breast cancer (HR: 1.0; 95% CI: 0.79, 1.43[31]; HR: 0.96; 95% CI: 0.76, 1.2[32]; HR: 1.0; 95% CI 0.82, 1.3[33]). Re-analyses of two randomized clinical trials showed no beneficial effect of metformin versus rosiglitazone on breast cancer risk but were limited by small numbers of breast cancer cases (n<20).[34] In contrast, in a cohort study from the Netherlands, the risk of breast cancer was slightly lower among metformin initiators compared with sulfonylureas initiators (HR: 0.95; 95% CI: 0.91, 0.98).[35] However, this study included women age 18 or older, representing a much younger study population than our Medicare-based cohort. Metformin might act differently on breast cancer in pre- and postmenopausal women. The Women's Health

Initiative study found a reduced risk of invasive breast cancer associated with metformin in post-menopausal women (HR: 0.75; 95% CI: 0.57, 0.99).[36] Drug exposures in the Women's Health Initiative study were self-reported and collected through questionnaires with unequal intervals, likely impeding the accurate identification of the date of treatment initiation.[19] Our study used data on pharmacy-dispensed prescriptions that provide longitudinal drug data, which enables the clear identification of initiators of drugs and to address issues related to the time since drug initiation.[37]

Our findings suggest that metformin may be associated with a lower risk of breast cancer among African American women, although this estimate was imprecisely measured. African Americans are more likely to develop triple receptor-negative breast cancer than white women.[38,39] One cohort study of 130 patients with triple receptor-negative breast cancer found that use of metformin was associated a lower risk of distant metastases (HR: 0.61; 95% CI: 0.33, 1.15)[40], supported by preclinical studies.[41,42] One plausible explanation for these findings is that metformin may have a favorable effect on triple receptor-negative breast cancer which is more prevalent in African Americans. In the Women's Health Initiative study, metformin use was associated with a greater reduction in the risk of human epidermal receptor 2 (HER2)-negative breast cancer (HR: 0.58; 95% CI: 0.40, 0.84), compared with overall invasive breast cancer (HR: 0.75; 95% CI: 0.57, 0.99), despite the fact that the two CIs overlapped.[36] Our subgroup analysis is limited by the small number of breast cancers in African American women observed, thus chance is a plausible alternative explanation.

We used external information from the MCBS to quantify the unmeasured confounding by BMI and smoking on the association between metformin and breast cancer incidence. Obesity and smoking were associated with higher odds of receiving metformin vs sulfonylureas. However, these associations became weak after adjusting for other variables in the propensity score model, indicating minimal independent effect of BMI and smoking of metformin prescribing relative to sulfonylureas and little residual confounding by BMI and smoking on the association between metformin and breast cancer incidence. This lack of effect on relative prescribing given the indication to initiate treatment with oral anti-diabetic drugs is a direct result of the state-of-the art new user, active comparator cohort design.[43] We consistently observed no metformin–breast cancer associations after implementing propensity score calibration. We acknowledge the possibility that similar results before and after applying propensity score calibration may be due to inadequate control using propensity score calibration. However, we observed little difference in BMI and smoking after controlling for other measured variables, indicating low potential for unmeasured confounding due to BMI and smoking.

Our study has several limitations. First, it is limited by the short follow-up time (maximum of 4.5 years). Diabetes treatment regimens are usually modified over time for adequate glycemic control as diabetes progresses, so the observed duration on the initial treatment is limited by actual treatment dynamics (median: 0.86 year; interquartile range: 0.38, 1.8) in the as-treated analysis. In the intention-to-treat analysis that ignored treatment changes during follow-up, the follow-up time was double (median: 1.8 years; interquartile range: 0.82, 3.1), but still short for evaluating a cancer outcome. Thus, we cannot exclude the

possibility of a beneficial effect of long-term use of metformin on breast cancer risk. Secondly, we have used a new user design with an active comparator to reduce confounding by indication. However, sulfonylureas are not recommended as the first-line treatment and the washout period to define new use is relatively short. Thus, our study population may include some patients with prior treatment and sulfonylurea initiators may have more severe diabetes on average than metformin initiators. This could lead to a lower baseline risk of breast cancer in metformin initiators resulting in a reduced HR but cannot explain our finding. Thirdly, we only started follow-up after the second dispensed prescription (i.e., the index date) because patients with a second prescription are more likely to be actually exposed to the drug. This may have introduced some selection bias but increases the likelihood that the patients actually took the drugs of interest. We also calculated percentage of days covered within the first year after initiation as a proxy of adherence among patients who continued treatment for ≥12 months and found no difference in adherence (eTable 7).

Our results may be confounded by unmeasured risk factors for breast cancer if these risk factors had an effect on choosing between metformin and sulfonylureas independent of all measured covariates. Unmeasured risk factors for breast cancer included BMI, smoking, alcohol use, family history of breast cancer, parity, and age at first birth. We examined the impact of two major unmeasured confounders, BMI and smoking using the MCBS survey and found that these did not affect choice of antidiabetic treatment, suggesting little potential for unmeasured confounding. Unfortunately, the MCBS survey did not capture information on all known risk factors for breast cancer.

This study is also limited due to lack of data on breast cancer subtypes. BMI was found to be associated with hormone receptor–positive breast cancer among postmenopausal women, but not other subtypes.[44,45] Thus, without breast cancer subtype data, we were unable to further explore the association between metformin, BMI, and subtypes of breast cancer. Despite the fact that not all Medicare beneficiaries enroll in part D drug plans, our results can be generalized to US older women or older Caucasian women residing in other countries. Given the small size of women of Black or other races in our study and subtype breast cancer varied by age and race, future research in Black, other races, and younger populations is warranted.

Another limitation is detection bias due to differential utilization of screening mammography. We examined the frequency of patients who underwent screening for breast cancer and found that metformin initiators were more likely to be screened for breast cancer before and after initiation (eTable 8). Greater utilization of screening mammography in metformin initiators before initiation may lead to a lower risk of breast cancer in metformin initiators at the time of starting follow-up because more women with asymptomatic breast cancer are excluded due to screening. This cannot explain our finding of no association between metformin and breast cancer. On the other hand, greater utilization of screening mammography in metformin initiators after initiation would lead to more breast cancer cases detected shortly after treatment initiation. As a result, metformin initiators may have an increased risk of breast cancer immediately following treatment initiation but a lower risk of breast cancer after the initial period compared with sulfonylureas initiators. We examined

the effect of metformin on breast cancer over time (Figure 1 and eFigure 4) and did not observe this pattern.

In conclusion, our findings suggest that initiation of metformin may not be associated with a short-term reduction in the risk for breast cancer among women aged 65 years or older when compared with initiation of sulfonylureas. We acknowledge that our study is limited by a short treatment and follow-up time, the former mainly a function of real-world treatment dynamics in older adults with type 2 diabetes. Randomized clinical trials have been initiated to evaluate metformin's benefit on cancer incidence and will provide more definitive answers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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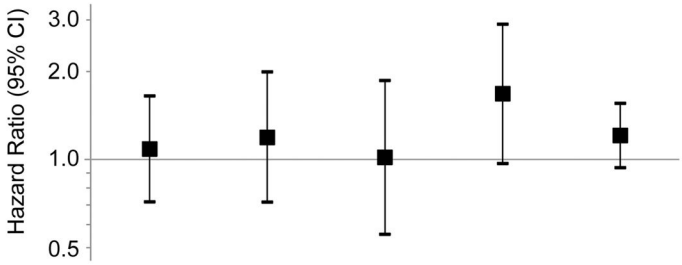
A



Follow-up (months)	0-6	7-12	13-18	19+	Overall
Initiators, n					
Metformin	45,900	30,841	21,132	14,714	45,900
Sulfonylurea	13,904	8,863	5,809	3,964	13,904
Breast Cancer Cases, n					
Metformin	137	90	54	104	385
Sulfonylurea	35	23	17	20	95
Estimates					
Weighted HR	1.1	1.2	1.0	1.7	1.2
95% Lower Limit	0.72	0.72	0.56	0.97	0.94
95% Upper Limit	1.7	2.0	1.9	2.9	1.6

B

Group	Metformin Pt N	Metformin Cases	Sulfonylurea Pt N	Sulfonylurea Cases	HR (95% CI)
Age, year					
60-69	13,248	90	2,929	19	1.0 (0.57, 1.8)
70-74	9,392	77	2,109	14	1.3 (0.67, 2.4)
75+	13,724	103	6,690	44	1.1 (0.76, 1.6)
Use of Statins					
Yes	20,267	149	5,411	33	1.3 (0.81, 1.9)
No	16,097	121	6,317	44	0.97 (0.66, 1.4)
Race					
White	28,853	225	9,086	58	1.2 (0.88, 1.7)
African American	3,858	23	1,589	13	0.79 (0.39, 1.6)

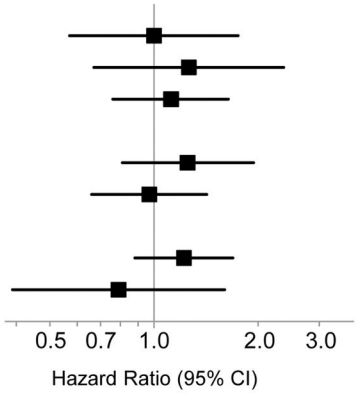


Figure 1.

Propensity score weighted hazard ratios (HR) and 95% confidence intervals (CIs) comparing metformin initiators vs sulfonylureas initiators since follow-up in the as-treated analysis, stratified by follow-up time (A) and by age group, race, and baseline use of statins (B). The results based on the intention-to-treat analysis are shown in eFigure 4.

Table 1

Characteristics of New Users of Metformin and Sulfonylureas at Baseline

	Metformin		Sulfonylureas		Weighted Sulfonylureas [a,b]
Characteristics	**No.**	**%**	**No.**	**%**	**%**
Total	45,900	100	13,904	100	100
Age, years					
65–69	17,057	37	3,600	26	37
70–74	11,814	26	2,495	18	24
75–79	7,929	17	2,404	17	18
80–84	5,211	11	2,407	17	13
85+	3,889	8	2,998	22	9
Race					
White	36,362	79	10,744	77	79
Black	4,917	11	1,889	14	11
Others	4,621	10	1,271	9.1	10
Comorbidity					
Benign Breast Disease	1,587	3.5	338	2.4	3.3
Benign neoplasm of breast	67	0.1	16	0.1	0.1
Chronic Obstructive Pulmonary Disease	3,416	7.4	1,344	10	7.9
Congestive Heart Failure	3,900	8.5	2,349	17	8.9
Ischemic Heart Disease	8,070	18	3,508	25	18
Hypertension	35,608	78	10,806	78	78
Osteoporosis	5,071	11	1,485	11	11
Medications					
Estrogen	2,772	6.0	575	4.1	5.8
Progestin	326	0.7	55	0.4	0.7
Statins	25,700	56	6,458	46	55
Bisphosphonates	5,227	11	1,350	10	12
ACE Inhibitors	17,194	37	5,138	37	38
ARBs	9,861	21	2,708	19	22
Beta Blockers	18,042	39	5,889	42	39

	Metformin		Sulfonylureas		Weighted Sulfonylureas [a,b]
Characteristics	**No.**	**%**	**No.**	**%**	**%**
Antidepressants	13,237	29	4,010	29	29
Digoxin	2,003	4.4	1,140	8.2	4.6
Calcium Channel Blockers	13,178	29	4,357	31	29
Loop Diuretics	7,078	15	3,470	25	16
Non-Loop Diuretics	18,438	40	4,721	34	40
Health Care Use					
Days of Hospitalization					
0	41,037	89	11,406	82	89
1 to 7	3,535	7.7	1,624	12	7.9
7 to 14	715	1.6	488	3.5	1.6
>14	613	1.3	386	2.8	1.4
Number of ER Visit					
0	37,259	81	10,229	74	81
1	5,920	13	2,343	17	13
2+	2,721	5.9	1,332	10	6.2
Number of Physician Visit					
0	3,170	6.9	1,494	11	7.3
1–3	11,653	25	3,704	27	26
4–6	11,447	25	3,162	23	24
7–12	12,197	27	3,515	25	26
13+	7,433	16	2,029	15	16
Mammography	9,170	20	1,792	13	20
Lipid Test	31,271	68	7,611	55	67

Abbreviation: ACE inhibitor: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blockers; ER: emergency room; IQR: interquartile range.

[a]Weighted by standardizing to their distribution in metformin initiators by using weights of 1 for metformin initiators and the odds of the estimated propensity score for sulfonylureas initiators. The propensity score model includes age in years (continuous variable), race (white, black, and others), comorbidity (Yes/No; benign breast disease, benign neoplasma of breast, chronic obstructive pulmonary disease, chronic heart failure, chronic kidney disease, acute kidney injury, ischemic heart disease, hypertension, and osteoporosis), medication use (Yes/No; estrogen, progestin, statins, bisphosphonates, ACE inhibitors, ARBs, beta blockers, antidepressant, digoxin, calcium channel clockers, loop diuretics, and non-loop diuretics), and healthcare utilization (days of hospitalization (continuous variable), number of physician visit (categorical variable), number of emergency room visit (categorical variable), mammograms (Yes/No), lipid tests (Yes/No), and calendar year of initiation).

[b] The plots of propensity score distributions before and after weighting are presented in the eFigure 2. In addition, we used standardized differences to evaluate the covariate balance between treatment groups (eFigure 3), and they were all <5%, suggesting the covariates between metformin and sulfonylureas initiators were balanced after propensity score weighting.

Table 2

Incidence Rates and Hazard Ratios for Breast Cancer by Treatment Cohort

Analysis	Cohort	No.	BC event	Follow-up Years		Crude Estimates				Weighted Estimates[a, b]			
				Median	IQR	Rate[c]	95% CI	HR	95% CI	Rate[c]	95% CI	HR	95% CI
AT[d]	MET	45,900	385	0.89	0.40, 1.9	6.5	5.9, 7.2	1.1	0.90, 1.4	6.5	5.9, 7.2	1.2	0.94, 1.6
	SUL	13,904	095	0.77	0.34, 1.7	5.8	4.7, 7.1	1.0		5.5	4.9, 6.2	1.0	
ITT	MET	45,900	603	1.80	0.81, 3.1	6.5	6.0, 7.1	1.1	0.93, 1.3	6.5	6.0, 7.1	1.2	0.96, 1.4
	SUL	13,904	170	1.90	0.85, 3.2	5.9	5.1, 6.8	1.0		5.7	5.2, 6.2	1.0	

Abbreviation: AT: as-treated analysis; BC: breast cancer; IQR: interquartile range; ITT: intention-to-treat analysis; MET: metformin; SUL: sulfonylureas.

[a] Propensity score weighted HR were standardized to the distribution of baseline covariates in metformin initiators

[b] We also performed a sensitivity analysis to account for competing risk of death using proportional subdistribution hazards model. The HR (95% CI) was 1.2 (0.95, 1.5) for the as-treated analysis, and 1.2 (0.99, 1.4) for the intention-to-treat analysis.

[c] The incidence rate of breast cancer per 1,000 person-years. Based on Surveillance, Epidemiology, and End Results Program (SEER) 2007–2011 data, the incidence rate of breast cancer for women aged 65 and over women is 4.2 cases per 1,000 person-years (1). We observed approximately 1.5-fold incidence rate of breast cancer in the initiators of metformin and sulfonylureas, likely explained by the diabetic study population in our study.

[d] In the as-treated approach, censoring occurred due to stopping, subsequent addition of, and switch to other anti-hyperglycemic drug classes (e.g., adding sulfonylureas or insulin to metformin) in 24%, 11%, and 6% of metformin initiators and in 25%, 21%, and 6% of sulfonylureas initiators, respectively.

Table 3

Characteristics of Metformin and Sulfonylurea Initiators at Baseline in the MCBS 2006–2009[a]

Characteristics	MET (N=118)	SUL (N=79)	Crude		Adjusted[d]	
			OR	95% CI	OR	95% CI
Median (IQR) of Age, years	74 (78, 80)	78 (75, 84)	0.92[c]	0.88, 0.96	0.94[c]	0.89, 0.99
Race, n (%)						
White	89 (75)	59 (75)	1.0	0.54, 2.0	0.85	0.40, 1.8
Other	29 (25)	20 (25)	1.0			
Median (IQR) of BMI, kg/m^2	30 (26, 34)	29 (25, 33)	1.0[b]	0.97, 1.1	--	
Mean (SD) of BMI, kg/m^2	30 (6.5)	30 (6.9)				
BMI Category, n (%)[b]						
<25	24 (20)	18 (23)	1.0			
25 to <30	35 (30)	30 (38)	0.87	0.40, 1.9	0.84	0.34, 2.1
≥30	58 (49)	29 (37)	1.5	0.70, 3.2	1.27	0.51, 3.1
Smoking Status, n (%)[b]						
Never Smoking	61 (52)	48 (61)	1.0			
Ever Smoking	57 (48)	28 (35)	1.6	0.89, 2.9	1.41	0.72, 2.7

Abbreviation: BMI: body mass index; IQR: interquartile range; MCBS: Medicare Current Beneficiary Survey; MET: metformin initiators; OR: odds ratio; SD: standard deviation; SUL: sulfonylureas initiators.

[a]Baseline characteristics between Medicare and MCBS new users were similar and are presented in eTable 6.

[b]Missing data on BMI and Smoking status were less than 5%. Our DUA does not allow us to present cell sizes <11, so the number of missing was not presented on this table.

[c]OR for 1 unit increase

[d]Adjusted OR was controlled for BMI (categorical), smoking status (never and ever), age, race (white and others), congestive heart failure, ischemic heart disease, beta blocker, anti-hypertensive drugs, loop diuretics, mammogram, admission to hospital, and physician visit in the propensity score model, as known as gold-standard propensity score in propensity score calibration method.